Docket No. 46745 (48340)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

APPLICANT:	J. Weidanz, et al.		
SERIAL NO.:	08/813,781	GROUP:	1644
FILED:	March 7, 1997	EXAMINER:	R. Schwadron

FOR: FUSION PROTEINS COMPRISING BACTERIOPHAGE COAT PROTEIN AND A SINGLE-CHAIN T CELL RECEPTOR

MS APPEAL BRIEF – PATENTS
COMMISSIONER FOR PATENTS
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I, Patricia A. Barnes, hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being deposited with the United States Postal Service with sufficient postage as "Express Mail Post Office To Addressee" service, **Label No. EV492344270US** in an envelope addressed to Mail Stop Appeal Brief – Patents, Commissioner for Patents, P. O. Box 1450, Alexandria, VA 22313-1450 on **March 25, 2005**.

Patricia A. Barnes

APPELLANTS' REPLY BRIEF PURSUANT TO 37 C.F.R. §1.193 (b)(1)

In reply to the Examiner's Answer dated January 26, 2005, submitted herewith is Appellants' Reply Brief.

For the benefit of the Board, Appellants now summarize the claimed invention and basis for the Examiner's outstanding rejection under §103.

SUMMARY OF THE CLAIMED INVENTION

The claimed invention features a soluble fusion protein engineered to include a bacteriophage coat protein (eg., fused to a single-chain T cell receptor ("scTCR"). The single-chain T cell receptor was itself designed to include an alpha-variable region ("V-α") fused to a beta-variable region ("V-β"). The single-chain T cell receptor forms a pocket that binds antigen when the antigen. The claimed soluble fusion protein is a single polypeptide chain with a beta-constant region ("C-β") region that is fused to V-β, for example.

Appellants discovered that by adding the bacteriophage coat protein to the claimed scTCR (ie., with the C-β region), it is possible to produce a fully soluble and functional scTCR. Unlike prior scTCRs, the claimed fusion proteins were found to be fully soluble, functional, and obtainable in significant quantities without difficulty. The claimed fusion proteins have a wide spectrum of important uses as described throughout the instant patent application.

SUMMARY OF THE EXAMINER'S OBVIOUSNESS REJECTION

As understood, the Examiner's obviousness rejection rests on the belief that it would be obvious to fuse Chung's scTCR to bacteriophage coat protein reported by Barbas because, allegedly, Barbas and Onda teach TCR-bacteriophage coat fusion proteins and Huse discloses that fusion protein with such a coat can supposedly be made in bacteria.

For the Examiner's prima facie case to stand, it is imperative that he establish that: 1) The cited references, and particularly Barbas discloses or suggests fusing a bacteriophage coat protein to Chung's scTCR; 2) there is a settled role for the bacteriophage coat protein in making fusion proteins; and that 3) one could fuse Chung's scTCR to Barbas' coat protein with a reasonable expectation of success.

As pointed out in Appellants' Brief on Appeal, the Examiner has not supported his position on any of these grounds.

REMARKS

Appellants now respond to particular points raised in the Examiner's Answer.

On pgs. 7-8 of the Answer, the Examiner made the following points with respect to the instant obviousness rejection and Appellants' Brief on Appeal.

1. Barbas (col. 14, first complete paragraph) discloses use of "receptor protein" which can be, according to the Examiner's reading of the cited patent, "eg., single-chain or heterodimeric or single-chain heteromers". Fully functional recombinant sc-TCR "had been produced" as evidenced by the Chung et al. reference.

2. Chung et al. teach that it would be desirable to produce single chain TCR using phage display techniques that had already been used to produce single chain antibodies.

3. Chung et al teach that the GPI anchor is cleaved and that the soluble TCR still has all the antigen binding properties of the TCR. Thus according to the Examiner' understanding, the GPI anchor is not required for the soluble TCR to function, it is just used in one particular method of making the soluble TCR.

4. Barbas and Chung et al disclose use of phage display systems to produce single chain antibodies.

5. Holler et al. is not familiar with the prior art or they are ignoring the prior art for self-promotion.

Appellants reply as follows:

1. Barbas Does Not Teach or Suggest The Single-chain T-Cell (sc-TCR) Constructs Of The Pending Claims.

The sections cited by the Examiner in the Answer (Barbas at column 14, first two full paragraphs) are provided below as a convenience to the Board.

> D. Polypeptides
>
> In another embodiment, the present invention contemplates a polypeptide comprising an **insert domain** flanked by an amino-terminal secretion signal domain and a carboxy-terminal filamentous phage coat protein membrane anchor domain.
>
> Preferably, the polypeptide is a fusion protein having a **receptor domain** comprised of an amino acid residue sequence that defines the ligand binding domain of a receptor protein positioned between a prokaryotic secretion signal domain and a gene VIII-encoded (cpVIII) membrane anchor domain. In preferred embodiments, the receptor protein is a polypeptide chain of a heterodimeric receptor. Insofar as the polypeptide has a receptor domain, it is also referred to herein as a receptor. In other preferred embodiments the secretion signal domain is a pelB secretion signal as described herein.
>
> Preferred heterodimeric receptors include immunoglobulins, major histocompatibility antigens of class I or II, lymphocyte receptors, integrins and the like heterodimeric receptors.

There is simply no explicit teaching or suggestion from this limited disclosure that one of skill would understand "insert domain" and/or "receptor domain" to encompass Appellants' sc-TCR with a beta-constant region ("C-β") region. Taken with the entire Barbas patent (entitled ***Heterodimeric Receptor*** *Libraries Using Phagemids*), one of skill would view the quoted passage as referring to ***heterodimeric receptors*** ie., a two chain (dimer) molecule in which both chains are different from the other. See also the Appeal Brief, pages 7-8 and footnote 4. One of skill would not understand the passage to mean the single-chain TCR constructs of the pending claims.

The Examiner states in the Answer that Chung et al. "had already produced" fully functional single chain T cell receptors (containing Vα and Vβ). That is incorrect. The Chung et al. reference was published well after Barbas' filing date (October 12, 1994) and earliest priority date (April 10, 1991). One reading Barbas would know that the "insert domain" and/or

"receptor domain" disclosed by Barbas could not have been referring to Chung's constructs because Chung had not been published. Barbas does not (cannot) cite Chung or even contemplate anywhere in the patent specification Appellants' three-domain sc-TCR proteins as an "insert domain" and/or "receptor domain" according to the patent.

Nowhere does Barbas teach or show how to make or use Appellants' scTCR molecules with or without a fused bacteriophage coat protein.

Even if the Board agrees with the Examiner's understanding of Barbas, as relied on, the patent does not show or even suggest how to make and use Appellants' claimed molecules

2. Chung et al. Merely Disclose That It "*May Be*" Useful To Make Single Chain TCR Molecules Using Phage Display Techniques

The section referred to by the Examiner in his Answer (pg. 12658, first column, first paragraph) is cited below as a convenience to the Board.

A scTCR molecule was designed which contains the V domains of both α and β chains and the C domain of the β chain. This scTCR molecule could be stably expressed at a high level in eukaryotic cells and could be isolated in a soluble form by enzymatic cleavage and affinity chromatography. The V_α and V_β domains appeared to be properly paired, since the scTCR bound to a conformation-dependent mAb, the superantigen SEB, and the proper MHC/peptide ligand. This design of scTCR offers an alternative to the two-chain design of soluble TCRs and has several advantages. (i) The sc design avoids the low-efficiency dimerization process which may be the limiting step in the assembly of TCR heterodimers from α and β subunits made in *Escherichia coli*. The sc design therefore allows efficient expression of the recombinant protein in quantities suitable for structural analysis and for some diagnostic or therapeutic applications. (ii) The design avoids the problems associated with the unstable expression of the human TCR α chain that have hindered efficient expression of human TCR molecules in eukaryotic cells. (iii) **The sc design may allow the construction of TCR phage display libraries** similar to those made for sc antibodies (28, 31). **scTCR phage libraries may be powerful tools** for the isolation of TCRs with defined specificities and/or high affinity for selective targeting of malignant and virally infected cells and for analyzing the interactions among TCR, MHC/peptide complexes, and superantigens.

At best, the section of Chung et al. cited by the Examiner is nothing more than an invitation to experiment. There is no specific disclosure (even taken with the other cited references) about how to make or use Appellants' soluble fusion protein.

More generally, the Examiner's position apparently rests on the unsupported assumption that a worker would know to use **single-chain antibody phage display** technology to make the claimed invention. See footnote 2 of Appellants' Brief (defining "phage display"). That assertion is not only unsupported but it is incorrect. That is, requirements for displaying scTCR molecules on bacteriophage are different than those for displaying single-chain antibodies

For example, Chung et al. as relied on states that sc design ***may allow*** the construction of TCR phage display libraries similar to those made for sc antibodies. Clackson and McCafferty are cited by Chung as teaching use of single-chain antibody phage libraries. But Clackson and McCafferty describe use phage display for making two-domain single-chain antibodies. Chung et al. as cited does not disclose or suggest how to use or adapt those teachings to make Appellants' invention ie., a fusion protein that includes a three-domain single-chain TCR.

Appellants cannot stress enough that the Holler reference (discussed below and in the Brief) states that "Phage display (citing the Clackson et al. work referenced by Chung) **has not proven successful** in the engineering of single-chain TCRs despite extensive structural similarity between antibody and TCR V regions". [1] Thus others in the field were dissuaded from using antibody phage display technology to make single-chain TCR molecules. Rather, it is Appellants who discovered how to do this. Not the work cited by the Examiner.

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[1] Appellants note that Holler correctly referenced Clackson et al's work as appearing (1991) Nature (London) Vol. 352: 624-628. The reference to the journal *Science,* cited by Chung et al. is incorrect.

Thus, it is certainly not obvious from the cited references that the single-chain antibody technology referenced by Chung could be used at all to make Appellants' soluble fusion molecules as alleged by the Examiner.

3. Chung et al. Does Not Teach or Provide Any Suggestion That Their GPI Anchor Fragment Can Be Substituted With Bacteriophage Coat Protein

Chung et al. disclose that single-chain TCR can be linked to (glycosyl phosphatidylinositol) GPI to "anchor" the TCR to cell membranes. This reportedly helps expression. Implicit in the Examiner's comments about Chung is that the GPI anchor and the bacteriophage coat protein of Barbas are **interchangeable**. However there is nothing in the cited references that supports this conclusion. Substantial differences between Chung's GPI anchor and bacteriophage coat proteins have been discussed at pg. 18 of the Appeal Brief. The Examiner's Answer does not address this issue.

4. Although Barbas and Chung teach Phage Display, The References Do Not Show or Suggest How It Can Be Used To Make The Claimed Invention

The Examiner's Answer asssumes that phage display techniques used to make single-chain antibodies can also be used to made the claimed invention. However, he points to no specific teaching on how to do that other then mentioning certain structural similarities between the molecules. He also contends, without specificity, that "a variety of different molecules have been produced using phage display technology". What molecules have been produced and how does that relate to the claimed invention?

The Examiner's position that single-chain antibodies and single-chain TCRs are "close enough" to support the instant rejection is at odds with experience. For instance, single-chain antibodies and single-chain TCRs are different molecules. One binds antigen (sc-Ab) and the other is a synthetic receptor that binds ligand in the presence of another molecule (called an

MHC complex). Single-chain antibodies are two domain molecules, while the claimed invention is a three-domain molecule ie., V-α V-β, C-β. In form and function, they are distinct.

As already mentioned, the Examiner's Answer assumes, but provides no supporting evidence, that phage display systems used to make single-chain antibodies can also be used to make single-chain TCRs. Holler et al. state that the approach "has not proven successful" (citing Clackson's approach for making single-chain antibodies). The Answer did not address this issue at all.

5. The Examiner's Assertion That Holler Is Not Familiar With The Prior Art Or is Engaged In Self-Promotion Is Clearly Wrong.

Holler stated that "Phage Display (citing the Clackson et al. work referenced by Chung) **has not proven successful** in the engineering of single-chain TCRs despite extensive structural similarity between antibody and TCR V regions." The Examiner's Answer does not address this issue. Instead, the Examiner continues to reference Weidanz et al. (J. Imm. Methods 1998) as evidencing information of which Holler should have been aware. As Appellants stated in their Brief, **Weidanz is not prior art** and is not properly a basis for rejecting the instant claims. Appeal Brief at pgs. 18-19 and see footnote 4. The Examiner's continued reliance on this document as a basis for maintaining the rejection is clearly improper.

More generally, Appellant is not aware of any precedent of the Board or Federal Circuit that would allow the Examiner to disregard objective evidence of non-obviousness on grounds that he believes the authors are " not familiar with the prior art" or supposedly engaged in "self-promotion". As set forth on pgs. 18-19 of the Appeal Brief, Holler is highly probative of the difficulties the field faced in making the claimed invention. Respectfully, it must be given weight by the Board as they consider the merits of the instant rejection.

CONCLUDING REMARKS

The Examiner commented about the Huse reference at pg. 10 of the Answer. However, the Answer does not address the substantial shortcomings of the reference as pointed out at pgs. 15-16 of the Appeal Brief. For instance, Huse reported that some constructs harmed the bacteriophage that carried them.

The Examiner's Answer also provided comments on the Onda reference. As set forth in the Appeal Brief at pgs. 14-15, Onda reports fusion of a TCR alpha chain to a bacteriophage coat protein. The TCR alpha chain is merely a fragment of the larger constructs Appellants now claim. Onda viewed his constructs as **unusual and not typical of TCR-ligand interactions**. Some of Onda's constructs were reported to work and others did not. It is not seen how Onda renders the claimed invention obvious taken alone or with the other cited references.

Appellants submit that they have overcome the Examiner's obviousness rejection in the view of all the facts and argument of record in this case. Simply put, one of skill in this area would not be able to predict, with any reasonable expectation of success, how to make and use the claimed invention.

It was the Appellents hard work that led to the claimed invention. That invention is not obvious from the references cited by the Examiner. Holler is exemplary of the difficulties faced by those working in the field to make and use the claimed invention.

REQUEST FOR ORAL HEARING

Pursuant to 37 CFR §1.194 Appellants respectfully request the opportunity to be heard at oral hearing. A separate paper is being submitted along with this Reply Brief.

Although it is not believed that the present submission requires any fee for consideration of this submission by the Office (including the request for oral hearing), the

Examiner is authorized to charge such fee to our deposit account **04-1105** should such fee be deemed necessary.

Respectfully submitted,

Date: 25 March 2005

By: _____

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